Epidemiology/Population

Associations of Short-Term and Long-Term Exposure to Ambient Air Pollutants With Hypertension
A Systematic Review and Meta-Analysis

Yuanyuan Cai,* Bo Zhang,* Weixia Ke, Baixiang Feng, Hualiang Lin, Jianpeng Xiao, Weilin Zeng, Xing Li, Jun Tao, Zuyao Yang, Wenjun Ma, Tao Liu

Abstract—Hypertension is a major disease of burden worldwide. Previous studies have indicated that air pollution might be a risk factor for hypertension, but the results were controversial. To fill this gap, we performed a meta-analysis of epidemiological studies to investigate the associations of short-term and long-term exposure to ambient air pollutants with hypertension. We searched all of the studies published before September 1, 2015, on the associations of ozone (O_3), carbon monoxide (CO), nitrogen oxide (NO_2 and NO), sulfur dioxide (SO_2), and particulate matter (PM_{10} and PM_{2.5}) with hypertension in the English electronic databases. A pooled odds ratio (OR) for hypertension in association with each 10 μg/m³ increase in air pollutant was calculated by a random-effects model (for studies with significant heterogeneity) or a fixed-effect model (for studies without significant heterogeneity). A total of 17 studies examining the effects of short-term (n=6) and long-term exposure (n=11) to air pollutants were identified. Short-term exposure to SO_2 (OR=1.046, 95% confidence interval [CI]: 1.012–1.081), PM_{2.5} (OR=1.069, 95% CI: 1.003–1.141), and PM_{10} (OR=1.024, 95% CI: 1.016–1.032) were significantly associated with hypertension. Long-term exposure (a 10 μg/m³ increase) to NO_2 (OR=1.034, 95% CI: 1.005–1.063) and PM_{10} (OR=1.054, 95% CI: 1.036–1.072) had significant associations with hypertension. Exposure to other ambient air pollutants (short-term exposure to NO_2, O_3, and CO and long-term exposure to NO_2, PM_{2.5}, and SO_2) also had positive relationships with hypertension, but lacked statistical significance. Our results suggest that short-term or long-term exposure to some air pollutants may increase the risk of hypertension.

(Coronary artery disease is the leading cause of death in the world. It is responsible for ~30% of all deaths or ~17.5 million people in 2012.1 As the major risk factor for cardiovascular disease, hypertension has been identified as the most important cause of disability and the leading risk factor for death globally.2 Disease, hypertension has been identified as the most important cause of limitation based on short-term or long-term exposure.9–12 These no association or an association only for selected pollutants or shown an association,4–8 whereas other studies have found either an association between exposure to traffic-related air pollution and hypertension.14 However, this study included only cohort studies conducted in the Europe and mainly focused on the traffic-related air pollutants, which might limit the external validity of their findings. Therefore, more such meta-analyses are urgently needed.

The previous published studies on hypertension and air pollution can be broadly divided into 2 categories: short-term and long-term studies. The former estimate the acute effects of air pollution exposure and mostly include time-series analyses over a few days. The latter evaluate the chronic effects of air pollution, such as cohort survival analyses over years of exposure.15 The short-term and long-term effects of air pollution may have

Cardiovascular disease is the leading cause of death in the world. It is responsible for ~30% of all deaths or ~17.5 million people in 2012.1 As the major risk factor for cardiovascular disease, hypertension has been identified as the most important cause of disability and the leading risk factor for death globally.2 The causes of hypertension are complex and are related to genetic factors, lifestyle, diet structure, and environmental factors, including air pollution.3 Since the 1990s, many epidemiological studies have investigated the associations between air pollution exposure and hypertension. However, the results remain controversial. Some studies have shown an association,4–8 whereas other studies have found either no association or an association only for selected pollutants or limitation based on short-term or long-term exposure.9–12 These inconsistent and controversial results indicate the need to quantitatively synthesize and interpret the available evidence to provide more explicit information for policy decisions and clinical use. Meta-analysis is the most commonly used statistical technique to quantitatively synthesize results from ≥2 separate studies.13 To our knowledge, there is only one meta-analysis that summarized the association between exposure to traffic-related air pollution and hypertension. However, this study included only cohort studies conducted in the Europe and mainly focused on the traffic-related air pollutants, which might limit the external validity of their findings. Therefore, more such meta-analyses are urgently needed.

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Key Words: air pollution ■ hypertension ■ long-term exposure ■ meta-analysis ■ short-term exposure

*These authors contributed equally to this work.

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nonmutually exclusive biological mechanisms, that is, direct and indirect effects on the sympathetic nervous system, oxidative stress, endothelial and other hemodynamic function, and vascular tone.16-19 Explicating the differences between the short-term and long-term effects of air pollution could provide further information for policy makers and clinical prevention for hypertension.

The aim of our study was to systematically review the associations between air pollutants and risk of hypertension and quantify the short-term and long-term effects of ambient air pollutants on hypertension risk using a meta-analysis. Our hypothesis was that an increase in ozone ($O_3$), carbon monoxide (CO), nitrogen oxide (NO and NO$_2$), sulfur dioxide (SO$_2$), particulate matter (PM$_{10}$), and PM$_{2.5}$ is associated with an increase in the risk of hypertension.

Methods

Search and Review Strategy

We searched the MEDLINE, PUBMED, Web of Science, EMBASE, China Biological Medicine, and Wanfang databases for all of the studies published before September 1, 2015. Our search strategy used a combination of keywords related to air pollution exposure (air pollution, particulate matter, fine particulate matter, particles, fine particles, carbon monoxide, nitrogen dioxide, nitrogen oxide, sulfur dioxide, ozone, CO, PM, PM$_{10}$, PM$_{2.5}$, SO$_2$, NO$_2$, NO$_x$, $O_3$, NO$_x$) and hypertension (high blood pressure, hypertension, high BP, and hypertensive disease). We also manually searched the references of every primary study for additional publications. Further publications were also identified by examining the review articles. Only publications in English were included in this study.

Study Selection

Two reviewers (Yuanyuan Cai and Bo Zhang) independently searched and selected all of the studies. They initially screened all of the study titles and abstracts. Studies were excluded if they did not address the associations between air pollutants and hypertension. The remaining studies were marked as potentially eligible, and their full texts were further evaluated. Only the studies that defined hypertension using at least one of the following definitions were included: (1) systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg; (2) use of antihypertensive drugs; (3) self-reported doctor-diagnosed hypertension; (4) definition according to the International Classification of Disease, 10th revision for hypertension (ICD10: I10), or (5) definition...
Table 1. Studies on the Associations of the Short-Term Exposure to Main Air Pollutants and Hypertension Risk

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Location</th>
<th>Study Duration</th>
<th>Study Design</th>
<th>Data Source</th>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>Definition of Hypertension</th>
<th>Air Pollutants</th>
<th>N-O Score</th>
</tr>
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<tr>
<td>Guo et al6</td>
<td>Beijing, China</td>
<td>2007</td>
<td>Case-crossover</td>
<td>Monitoring network and self-monitoring data</td>
<td>-</td>
<td>1491</td>
<td>ICD10: 110</td>
<td>PM 2.5, PM 10</td>
<td>7</td>
</tr>
<tr>
<td>Guo et al6</td>
<td>Beijing, China</td>
<td>2007</td>
<td>Case-crossover</td>
<td>Monitoring network data</td>
<td>-</td>
<td>1491</td>
<td>ICD10: 110</td>
<td>SO 2, NO 2</td>
<td>7</td>
</tr>
<tr>
<td>Costa et al22</td>
<td>São José dos Campos, Brazil</td>
<td>2007–2010</td>
<td>Time-series</td>
<td>Monitoring network data</td>
<td>†</td>
<td>606</td>
<td>ICD10: 110-115</td>
<td>PM 10</td>
<td>2</td>
</tr>
<tr>
<td>Qorbani et al22</td>
<td>Tehran Islamic Republic of Iran</td>
<td>2007</td>
<td>Case-crossover</td>
<td>Monitoring network data</td>
<td>-</td>
<td>250</td>
<td>Systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or use of antihypertensive drugs</td>
<td>CO, PM 10</td>
<td>7</td>
</tr>
<tr>
<td>Szypszkowicz et al2</td>
<td>Edmonton, Canada</td>
<td>1992–2002</td>
<td>Case-crossover</td>
<td>Monitoring network data</td>
<td>-</td>
<td>5365</td>
<td>ICD9: 401</td>
<td>CO, NO 2, SO 2, O 3, PM 10, PM 2.5</td>
<td>7</td>
</tr>
</tbody>
</table>

- The number of controls was not available because this was a case-crossover study.

*Newcastle–Ottawa score.
†The number of controls was not available because these studies were time-series studies.

according to ICD9: 401. The studies were not included in this meta-analysis if they were animal studies, duplicates, reviews, case reports, case series, studies involving only blood pressure, and studies without original data or enough quantitative data. Disagreements about the eligible studies were resolved by a discussion between the authors.

A total of 56,877 records were identified through searching the database. After screening the titles, abstracts, bibliographic references, commentaries, and editorial of the articles, 167 studies were considered potentially eligible studies, and the full-text articles were retrieved and reviewed. Of these, 149 studies were further excluded because they were not related to hypertension and air pollution or they did not provide the dose–response relationship between air pollutants and hypertension (n=116), they did not provide sufficient data for analysis (n=31), or they were repeated studies (n=3). Finally, 17 studies were included in this meta-analysis and contained >108 thousand hypertension cases and 220 thousand controls.

The study selection process is presented in detail in Figure 1.

Quality Evaluation

All of the included studies were evaluated by a quality scale from New Castle Ottawa.20 Using this scale, each study is evaluated by 8 items that are categorized into 3 groups: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. Each item was graded for a maximum score of 1 point, except that related to comparability, which allowed for 2 points. The total score ranged from 0 points (lowest) to 9 points (highest), with a higher score indicating a higher quality. Two investigators were asked to evaluate the quality independently. In the case of a disagreement, a third investigator was consulted. In this study, the average Newcastle–Ottawa scores were 6.3, 6.0, and 6.5 for all 17 included studies, short-term and long-term exposure studies (Tables 1 and 2).

Data Extraction

We first divided all included studies into short-term and long-term studies. The former included time-series and case-crossover studies that assessed study subjects’ exposure to air pollution and estimated their acute effects on hypertension risk over several days.4,5,8,21,22 The latter were defined as studies that assessed study subjects’ average exposure to air pollution and evaluated their chronic effects over years, including cross-sectional, cohort, and case–control studies.4,5,8,21,22

We used a standardized table to extract the following information from all of the included articles: authors, publication year, study setting, study population, study duration, study design, short-term or long-term effect, exposure measurement method, data source, number of controls and cases, type of air pollution, exposure mean and range, adjusted odds ratio (OR) and their 95% confidence intervals (CIs), adjusted covariates, and the number of lag days for short-effect if applicable. Eligibility assessments and all of the data extraction were checked and verified by consensus of the 2 investigators. In a case of discordance, a third reviewer was asked to give his opinion.

Quantitative Data Synthesis

Before performing the meta-analysis, all of the air pollutant concentration units such as ppb (parts per billion) were transformed to μg/m3. After their risk estimates (ORs) were converted to a common exposure unit increase (10 μg/m3), we were able to summarize the estimates from different studies. To evaluate the short-term effects of air pollution exposure, some studies took into account different lag patterns using single-day lags from lag 0 to 7 days.4,5,8,22 Other studies have used both single-day lag and cumulative lag pattern.14 Nevertheless, most of the included studies used a single-day lag pattern. Thus, we used the single-day lag pattern to assess the associations between short-term exposure to air pollutants and hypertension risk. If several lag estimates were reported in the same article, we chose the most frequently used in the studies. In this study, we chose lag 1 for the short-term effects of O3 and CO, lag 2 for PM10, lag 3 for NO2 and SO2, and lag 6 for PM2.5. Long-term studies evaluated the long-term impact of chronic exposure to air pollutants on the risk of hypertension, such as cohort studies over years of exposure.24,25 All of the included studies verified the linearity assumption concerning the association between air pollutant exposure and hypertension risk.

Statistical Analysis

We used a meta-analysis model to quantitatively estimate the associations of short-term and long-term exposure to air pollutants with
Figure 2. Forest plots for the pooled associations between air pollutants (per 10 μg/m³ increment) and hypertension. A. The pooled effect estimate of short-term exposure to SO₂ on hypertension. B. The pooled effect estimate of short-term exposure to NO₂ on hypertension. C. The pooled effect estimate of short-term exposure to PM₂.₅ on hypertension. D. The pooled effect estimate of short-term exposure to PM₁₀ on hypertension. E. The pooled effect estimate of long-term exposure to NO₂ on hypertension. F. The pooled effect estimate of long-term exposure to NOₓ on hypertension. G. The pooled effect estimate of long-term exposure to PM₂.₅ on hypertension. H. The pooled effect estimate of long-term exposure to PM₁₀ on hypertension.
Table 2. Studies on the Associations of the Long-Term Exposure to Main Air Pollutants and Hypertension Risk

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Location</th>
<th>Study Duration</th>
<th>Study Design</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babisch et al23</td>
<td>Greater Augsburg, Germany</td>
<td>2008–2009</td>
<td>Cross-sectional</td>
<td>Monitoring network data Land use regression model</td>
</tr>
<tr>
<td>Chan et al8</td>
<td>Taiwan</td>
<td>2001–2005</td>
<td>Cross-sectional</td>
<td>Monitoring network data</td>
</tr>
<tr>
<td>Chen et al19</td>
<td>Ontario, Canada</td>
<td>1996–2010</td>
<td>Cohort study</td>
<td>Monitoring network data</td>
</tr>
<tr>
<td>Chen et al22</td>
<td>Taipei, Taiwan</td>
<td>2009</td>
<td>Cross-sectional</td>
<td>Monitoring network data</td>
</tr>
<tr>
<td>Coogan et al24</td>
<td>Los Angeles, USA</td>
<td>1995–2005</td>
<td>Cohort study</td>
<td>Monitoring network data</td>
</tr>
<tr>
<td>Foraster et al26</td>
<td>Girona, Spain</td>
<td>2009–2011</td>
<td>Cohort study</td>
<td>Monitoring network data</td>
</tr>
<tr>
<td>Johnson and Parker27</td>
<td>USA</td>
<td>1999–2005</td>
<td>Cross-sectional</td>
<td>Monitoring network data</td>
</tr>
<tr>
<td>Sørensen et al29</td>
<td>Denmark</td>
<td>2000–2002</td>
<td>Cohort study</td>
<td>Dispersion model</td>
</tr>
</tbody>
</table>

(Continued)

hypertension risk. To explore the possible heterogeneity between the study results, we hypothesized that the effect size might differ according to the methodological quality of the studies. The heterogeneity of the included studies was evaluated by using the Q statistic and F statistic. Cochran’s Q statistic was calculated by summing the squares of the deviations of the estimates from each study of the overall meta-analysis estimate by weighting each study’s contribution. A P value was obtained by comparing the Q statistic with a χ² distribution with k–1 degrees of freedom, where k was the number of included studies.69 If the P value was <0.05, then a random-effects model was selected; otherwise, a fixed-effect model was selected. The F statistic \[P = (Q – df)/Q_0 \times 100\] describes the percentage of the variation across the studies that is because of heterogeneity rather than chance. A value of F<50% demonstrated that there is a statistically significant heterogeneity.69 To test the impacts of methods selection on the results of meta-analyses, we separately estimated the combined effects of air pollutants using a random-effects model and a fixed-effect model.71 We also used funnel plot asymmetry to detect the potential publication bias. An Egger’s regression was applied to test the funnel plot symmetry, in which the inverse of the standard error was the independent variable and the standardized estimate of the effect size was the dependent variable.71

We also used a series of sensitivity analyses to test the robustness of our results. Because some meta-analyses included few studies, we only conducted sensitivity analyses for the meta-analyses that included >3 studies. For each sensitivity analysis, we individually removed the single studies with the largest and the smallest estimates from the meta-analyses.

Finally, a meta-regression model was used to investigate the possible modification effects of age on the effect sizes of air pollution, which could provide more information on the sources of heterogeneity between included studies.

All of the statistical tests were 2-sided, and P<0.05 was considered statistically significant. We used R software (version 3.2.2; R Development Core Team 2012, www.R-project.org) to analyze the data, and the package metafor was used.

Results

Definition of Hypertension

Of the 17 included studies, 3 studies defined hypertension as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg4,24,25; 5 studies defined hypertension according to the ICD9 or ICD10 code4,22,23; 2 studies used self-reported doctor-diagnosed hypertension5,27; and 7 studies used >1 methods to define the hypertension cases4,10,12,21,23,26,28,29 (Tables 1 and 2).

Assessment of Air Pollution Exposure Measurements

Most of the studies (12/17) assessed the air pollutant concentrations using routine air pollution data from central air pollution monitoring stations.4,6,7,9,10,12,21,22,24–26 The air pollutant concentrations were selected from the monitoring station nearest to the individual’s residence or were calculated using the average concentrations in a region where there were >1 monitoring stations. Four studies assessed the air pollution exposure using complex dispersion models or land use regression models that included various databases, including traffic, meteorology, roadway geometry, vehicle emission, air quality monitoring data, and land use.5,23,28,29 These models could estimate each subject’s exposure level with high accuracy. One study used both data from central air pollution monitoring stations and self-monitoring data8 (Tables 1 and 2).

Associations Between Short-Term Exposure to Air Pollutants and Hypertension Risk

A total of 6 studies investigated the relationships between short-term exposure to air pollutants and hypertension.6,9,21,22 Of these studies, 5 were case-crossover studies and one was time-series study. Two studies were conducted in China, 2 in Canada, and 2 in Brazil and Iran. Four studies evaluated PM₁₀ and 3 evaluated SO₂, NOₓ, or PM₂.⁵ The number of lag days ranged from 1 to 7 per pollutant and per study (Table 1).

The results of meta-analyses showed that hypertension was significantly associated with short-term exposure to SO₂...
Table 2. Continued

<table>
<thead>
<tr>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>Definition of Hypertension</th>
<th>Air Pollutants</th>
<th>N-O Score*</th>
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<tbody>
<tr>
<td>2614</td>
<td>1552</td>
<td>Systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg, self-reported doctor-diagnosed hypertension or use of antihypertensive drugs in conjunction with self-reported doctor diagnosed hypertension</td>
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<tr>
<td>12658</td>
<td>6209</td>
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<td>SO$<em>2$, PM$</em>{2.5}$, NO$_2$</td>
<td>7</td>
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<tr>
<td>35303</td>
<td>10945</td>
<td>ICD10:I10-I13 (+15 after 2002) or ICD9: 401–405</td>
<td>PM$_{2.5}$</td>
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<tr>
<td>10324</td>
<td>17422</td>
<td>Systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg or self-reported doctor-diagnosed hypertension</td>
<td>NO$<em>2$, PM$</em>{2.5}$, PM$_{10}$, NO$_x$</td>
<td>5</td>
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<tr>
<td>3236</td>
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<td>PM$_{2.5}$, NO$_x$</td>
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<tr>
<td>16188</td>
<td>8657</td>
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<td>PM$_{2.5}$, SO$_2$, NO$_x$, O$_3$</td>
<td>6</td>
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<td>NO$_2$</td>
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<tr>
<td>98839</td>
<td>35405</td>
<td>Self-reported doctor-diagnosed hypertension</td>
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<td>961</td>
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<td>3982</td>
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<td>36235</td>
<td>8201</td>
<td>Self-reported doctor-diagnosed hypertension or use of antihypertensive drugs</td>
<td>NO, NO$_2$, NO$_x$</td>
<td>7</td>
</tr>
</tbody>
</table>

*Newcastle–Ottawa score.

(OR=1.046, 95% CI: 1.012–1.081), PM$_{2.5}$ (OR=1.069, 95% CI: 1.003–1.141), and PM$_{10}$ (OR=1.024, 95% CI: 1.017–1.030) in each 10 μg/m$^3$ increment. We also observed a marginally statistically significant association between short-term exposure NO$_x$ (OR=1.037, 95% CI: 0.994–1.082) and hypertension risk (Figure 2). In particular, there were only 2 studies that explored the effects of short-term exposure to CO and O$_3$ on hypertension, which limited us to summarize the pooled effect estimates using a meta-analysis. For the 2 studies that investigated the short-term effects of CO, neither Szyszkwicz et al (OR=1.0002, 95% CI: 0.9992–1.0012) nor Qorbani et al (OR=1.0008, 95% CI: 0.9985–1.0031) found significant results. For the 2 studies that assessed the short-term effects of O$_3$, none of them (OR=1.007 [95% CI: 0.980–1.032] for Szyszkwicz et al’s study and OR=1.000 [95% CI: 0.969–1.032] for Brook et al’s study) found significant associations.

Associations Between Long-Term Exposure to Air Pollutants and Hypertension Risk

Eleven studies assessed the associations of long-term exposure to air pollutants with hypertension. Of these studies, the most common epidemiological designs were cross-sectional (n=5) and cohort studies (n=4). Two other studies were case–control designs. Three studies were conducted in China, 2 in the United States, 2 in Sweden, and 4 in Germany, Spain, Canada, or Denmark. Six studies evaluated the effects of NO$_x$, 5 studies evaluated PM$_{2.5}$, 4 evaluated NO$_2$, and 3 evaluated PM$_{10}$ (Table 2). There was a statistically significant increase in hypertension risk in association with each 10 μg/m$^3$ increment in long-term exposure to NO$_x$ (OR=1.034, 95% CI: 1.005–1.063) and PM$_{2.5}$ (OR=1.034, 95% CI: 1.005–1.063). We did not find statistically significant associations of hypertension with NO (OR=1.127, 95% CI: 0.933–1.361) and PM$_{10}$ (OR=1.065, 95% CI: 0.985–1.152), but their OR values indicated the possible increased risks of hypertension associated with NO$_x$ and PM$_{2.5}$ exposure (Figure 2). Only 2 studies assessed the long-term effects of SO$_2$ on hypertension, but both of them observed statistically significant associations. Chan et al observed a 73.2% increase (OR=1.732, 95% CI: 1.309–2.308) in hypertension risk associated with a 10 μg/m$^3$ increment in long-term exposure to SO$_2$, and Dong et al found that the OR between a 10 μg/m$^3$ increment in SO$_2$ concentration and hypertension was 1.054 (95% CI: 1.020–1.086).25

Sensitivity Analyses

The meta-analysis results were generally robust for the exclusion of single studies that had the largest or smallest effect size with regard to the significance of the estimated associations, but there was one exception (Figure S1 in the online-only Data Supplement). The pooled effect estimate (OR=1.065, 95% CI: 0.985–1.152) for hypertension, with a 10 μg/m$^3$ increase in long-term PM$_{2.5}$ exposure became statistically significant (OR=1.098, 95% CI: 1.015–1.188) after excluding the study with the smallest effect size. We also observed that selection of fixed-effect model or random-effects model did not significantly change the results of meta-analyses, although some CI of ORs were wider in some meta-analyses using a random-effects model (Figures S2 and S3).

Heterogeneity Analyses and Publication Bias Analyses

The heterogeneity analyses revealed that most of the meta-analyses did not have significant heterogeneity between included studies except for the analyses of short-term exposure to NO$_2$ and PM$_{2.5}$ and long-term exposure to NO$_x$ and PM$_{2.5}$ (Figure 2). Age might be an important source of heterogeneity between studies. The results of meta-regression analyses showed that the age of study population was significantly negatively associated with the effect sizes of long-term exposure to NO$_x$ ($\beta=-0.007$, $P=0.021$) and PM$_{2.5}$ ($\beta=-0.004$, $P=0.049$; Figure S4). The results of Egger’s tests showed that there was no significant publication bias in the meta-analyses (Figure S5).
Discussion

Hypertension remains a worldwide public health challenge.32,33 Ascertain the risk factors of hypertension could provide significant information for the prevention of hypertension and cardiovascular diseases.34 In this meta-analysis, we quantitatively assessed the associations between short-term and long-term exposure to ambient air pollutants and the risk of hypertension. We observed that short-term exposure to SO\(_2\), PM\(_{2.5}\), and PM\(_{10}\) and long-term exposure to NO\(_2\) and PM\(_{10}\) were associated with an increase in hypertension risk. To our knowledge, this is the first study to simultaneously estimate the effects of short-term and long-term exposure to air pollutants on hypertension by meta-analysis. Our findings are consistent with the results of 2 previous meta-analyses that summarized the associations between air pollution exposure during pregnancy and pregnancy-induced hypertensive disorders.35,36 Pedersen et al found that pregnancy-induced hypertensive disorders were significantly associated with a 5 μg/m\(^3\) increment in PM\(_{10}\) (OR=1.57; 95% CI: 1.26–1.96), a 10 μg/m\(^3\) increment in NO\(_2\) (OR=1.20; 95% CI: 1.00–1.44), and a 10 μg/m\(^3\) increment in NO\(_2\) (OR=1.13; 95% CI: 1.02–1.26).35 Given the enormous prevalence of hypertension37 and the ubiquitous nature of ambient air pollution exposure,38 we speculate that our findings between air pollutants and hypertension are of considerable and growing global public health importance.

The mechanisms by which air pollution exposure could contribute to the development of hypertension might include systemic inflammation and oxidative stress,39 which may cause increased sympathetic tone and potentially lead to arterial remodeling.40 Schins et al observed that when rats were exposed to PM\(_{2.5}\), their blood endotoxin content, interleukin-8 and tumor necrosis factor-α levels increased significantly.41 Oxidative stress may also increase the circulation of activated inflammatory cytokines, which may subsequently induce endothelial dysfunction, lead to an imbalance in vascular homeostatic response, and result in total peripheral resistance and a fixation of evaluated blood pressure.42,43 PM may also elevate blood pressure by inducing autonomic nervous system imbalance and vasoconstriction.24 In addition, PM exposure can also reduce daytime sodium excretion and blunt the normal nocturnal reduction in blood pressure. If this happens repeatedly, the impaired renal handling of excess sodium may partly contribute to elevated blood pressure.44

Discrepancies between the magnitudes of short-term and long-term exposure effects have been a particular concern in air pollution and health studies.45 In this study, we observed that the short-term PM\(_{10}\) exposure–hypertension association (OR=1.023, 95% CI: 1.017–1.029) was substantially lower than the equivalent long-term association (OR=1.054, 95% CI: 1.036–1.072). This result was consistent with certain previous study findings.44,45 For example, in the Renfrew–Paisley cohort study, Beverland et al found that a 10 μg/m\(^3\) increase in average black smoke over 3 days (short-term) was associated with a 1.8% (95% CI: 0.1%–3.4%) increase in all-cause mortality compared with an estimate of a 10% (95% CI: 4%–17%) increase in mortality risk for a 10 μg/m\(^3\) increase in average black smoke from 1970 to 1979 (long-term).45 This discrepancy might be because of several reasons. Short-term exposure studies capture only part of the total effects of long-term repeated exposure to air pollution.44 Some other authors proposed that the larger magnitudes of the association between long-term exposure and health may be attributable to cumulative effects that increase the sensitivity of highly exposed population subgroups.46 However, we also observed similar estimates in the magnitudes of the effects of short- and long-term exposures to PM\(_{2.5}\) and NO\(_2\). The reasons for these inconsistent results remain unclear and may be related to differences in study populations, lag patterns, races, regions, exposure assessment methods, the constituents of PM, and the confounders adjustment between studies.46,47 Therefore, more studies are needed in the future to explore the differences of short-term and long-term air pollution exposure effects on human health.

Our results also demonstrated that both short-term and long-term exposure to PM\(_{2.5}\) has a more pronounced effect than PM\(_{10}\) on hypertension risk in each 10 μg/m\(^3\) increase. Studies investigating the adverse effects of PM on other health outcomes, such as mortality48 and respiratory diseases,49 also observed these types of results. Compared with PM\(_{10}\), PM\(_{2.5}\) can remain suspended for a longer time in the air and be inhaled into the respiratory tract and directly into the pulmonary alveoli. In addition, PM\(_{2.5}\) has a larger superficial area and hence absorbs more chemical constituents than PM\(_{10}\). Therefore, PM\(_{2.5}\) is probably more harmful on human health than PM\(_{10}\).8,50

We did not find statistically significant associations of hypertension with short-term exposure to NO\(_2\) and long-term exposure to NO\(_2\). The lower statistical power caused by the fewer number of included studies may be one of the possible reasons. Only 3 and 4 studies were selected to estimate the pooled effects of NO\(_2\) and NO\(_2\) on hypertension, respectively. In particular, the associations of hypertension with short-term exposure to CO and O\(_3\) and long-term exposure to SO\(_2\) were independently assessed by only 2 studies. The number of the included studies was too small to permit us to quantitatively summarize the pooled associations by meta-analysis. However, a previous meta-analysis observed the significant associations of hypertensive disorders of pregnancy with CO and O\(_3\) exposure during the pregnancy.51 For example, a 1 ppm increase in average CO exposure during the first trimester was associated with a 79% (95% CI: 31%–145%) increase in the risk of hypertensive disorder during pregnancy.51 These results indicate that more research is needed in the future to confirm the possible effects of CO, O\(_3\), SO\(_2\), and NO\(_2\) on hypertension.

The results of the heterogeneity analyses showed significant heterogeneity for some analyses, including short-term exposure to NO\(_2\) and PM\(_{2.5}\) and long-term exposure to NO\(_2\) and PM\(_{2.5}\) analyses. However, all of the analyses showed increased ORs. Therefore, the heterogeneity reflected differences in the magnitude rather than differences in the direction of the associations. The heterogeneity between the included studies may reflect differences in the study settings, study design, exposure assessment, constituents of PM, and confounder adjustment, which may influence the variation in exposure to air pollution and potentially cause different dose–response relationships.46,47 In addition, we found that age was negatively associated with effect sizes of air pollution, which indicated that age might be an important source of heterogeneity between studies. The protective effect of age might be related to the different medication use between young age and elderly.52 It was found that older people usually use more medication than young people, and not taking medication was...
a strong predictor of increased blood pressure effects for both systolic and pulse pressure. To reduce the impact of heterogeneity, we used a random-effects model to combine the individual study’s finding. A subgroup analysis is an important tool to explore the sources of between-study heterogeneity. However, the few number (n<5) of included studies with significant heterogeneity prevented us from conducting such analyses.

Our study has several limitations that should be considered. First, there are few studies on air pollutants, such as CO and O₃, which prevented us from conducting a meta-analysis and subgroup analysis. We cannot rule out the possibility that our current results are chance findings and that the absence of publication bias is because of the relatively small number of included primary studies. Second, most included studies used a single-pollutant model despite the fact that there are possible interactions between pollutants. Multipollutant models are difficult to implement and validate. Therefore, we independently estimated the association between each pollutant and hypertension risk based on the single-pollutant model results and did not evaluate the interactions between the air pollutants. More studies are needed in the future to take into account more factors, such as individual-level covariates and interactions between pollutants, and to explore the source-specific effects of particulate matter, such as elemental compositions.

Perspectives
To our knowledge, this meta-analysis is the first study to assess the quality and magnitude of the associations between air exposure and the risk of hypertension. Our results provide strong evidence that both short-term and long-term exposure to the main air pollutants increases the risk of hypertension. Our findings are of public health importance because both air pollution and hypertension are important worldwide public health problems. Even though a small risk of hypertension is induced by the air pollution exposure, it may bring a large population-attributable disease burden of hypertension because of the ubiquitous nature of air pollution. Therefore, if these exposures are avoided, they theoretically could reduce the incidence of hypertension.

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Disclosures
None.

References


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Associations of short-term and long-term exposure to ambient air pollutants with hypertension: A systematic review and meta-analysis

Yuanyuan Cai, Bo Zhang, Weixia Ke, Baixiang Feng, Hualiang Lin, Jianpeng Xiao, Weilin Zeng, Xing Li, Jun Tao, Zuyao Yang, Wenjun Ma, Tao Liu
Figure S1. Sensitivity analyses for the pooled estimates of the air pollutants (per 10μg/m³ increment) on hypertension risk.

A: All studies were included; B: The study with the largest effect size was excluded; C: The study with the smallest effect size was excluded.
Figure S2. Forest plots for the pooled associations between air pollutants (per 10 μg/m³ increment) and hypertension estimated by fixed effects models.
A: Short-term exposure to SO$_2$

B: Short-term exposure to NO$_2$

C: Short-term exposure to PM$_{2.5}$

D: Short-term exposure to PM$_{10}$

E: Long-term exposure to NO$_2$

F: Long-term exposure to NOx

G: Long-term exposure to PM$_{2.5}$

H: Long-term exposure to PM$_{10}$

Figure S3. Forest plots for the pooled associations between air pollutants (per 10 μg/m$^3$ increment) and hypertension estimated by random effects models.
Figure S4. Meta-regression analysis on the modification effects of age on the associations between air pollution exposure (per 10 μg/m³ increment) and hypertension
Figure S5. Funnel plots for the meta-analyses assessing the associations between air pollutants (per 10 \(\mu g/m^3\) increment) and hypertension.